CLAIMS

We claim:

1. A targeting construct comprising:

   (a) a first polynucleotide sequence homologous to an ubiquitin ligase E3 gene;

   (b) a second polynucleotide sequence homologous to the ubiquitin ligase E3 gene; and

   (c) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

3. A method of producing a targeting construct, the method comprising:

   (a) providing a first polynucleotide sequence homologous to an ubiquitin ligase E3 gene;

   (b) providing a second polynucleotide sequence homologous to the ubiquitin ligase E3;

   (c) providing a selectable marker; and

   (d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

4. A method of producing a targeting construct, the method comprising:

   (a) providing a polynucleotide comprising a first sequence homologous to a first region of an ubiquitin ligase E3 gene and a second sequence homologous to a second region of an ubiquitin ligase E3 gene;

   (b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.

5. A cell comprising a disruption in an ubiquitin ligase E3 gene.

6. The cell of claim 5, wherein the cell is a murine cell.

7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.

8. A non-human transgenic animal comprising a disruption in an ubiquitin ligase E3 gene.

9. A cell derived from the non-human transgenic animal of claim 8.

10. A method of producing a transgenic mouse comprising a disruption in an ubiquitin ligase E3 gene, the method comprising:

(a) introducing the targeting construct of claim 1 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

11. A method of identifying an agent that modulates the expression of an ubiquitin ligase E3, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in an ubiquitin ligase E3 gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of ubiquitin ligase E3 in the non-human transgenic animal is modulated.

12. A method of identifying an agent that modulates the function of an ubiquitin ligase E3, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in an ubiquitin ligase E3 gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted ubiquitin ligase E3 gene in the non-human transgenic animal is modulated.

13. A method of identifying an agent that modulates the expression of ubiquitin ligase E3, the method comprising:

(a) providing a cell comprising a disruption in an ubiquitin ligase E3 gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the ubiquitin ligase E3 is modulated.

14. A method of identifying an agent that modulates the function of an ubiquitin ligase E3 gene, the method comprising:

(a) providing a cell comprising a disruption in an ubiquitin ligase E3 gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the ubiquitin ligase E3 gene is modulated.

15. The method of claim 13 or claim 14, wherein the cell is derived from the non-human transgenic animal of claim 8.

16. An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.

17. A transgenic mouse comprising a disruption in an ubiquitin ligase E3 gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: embryonic lethality; arrested development; and small, abnormal or reabsorbing egg cylinders.

18. The transgenic mouse of claim 17, wherein development is arrested at embryonic day 8.5.

19. The transgenic mouse of claim 17, wherein homozygous offspring are undetectable after embryonic day E8.5.

20. The transgenic mouse of claim 17, wherein the egg cylinders fail to develop somites.

21. The transgenic mouse of claim 17, wherein the wherein the egg cylinders are reabsorbed by embryonic day 8.5.

22. The transgenic mouse of claim 21, wherein the abnormal egg cylinders at embryonic day 7.5 resemble normal embryonic day 8.5 egg cylinders.

23. A method of producing a transgenic mouse comprising a disruption in an ubiquitin ligase E3 gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: embryonic lethality; arrested development; and small, abnormal or reabsorbing egg cylinders,

the method comprising:

(a) introducing an ubiquitin ligase E3 gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in an ubiquitin ligase E3 gene.

24. A cell derived from the transgenic mouse of claim 17 or claim 23.

25. A method of identifying an agent that ameliorates a phenotype associated with a disruption in an ubiquitin ligase E3 gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in an ubiquitin ligase E3 gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: embryonic lethality; arrested development; and small, abnormal or reabsorbing egg cylinders.

26. A method of identifying an agent that modulates ubiquitin ligase E3 expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in an ubiquitin ligase E3 gene; and

(b) determining whether the agent modulates ubiquitin ligase E3 expression in the transgenic mouse, wherein the agent has an effect on at least one of the following phenotypes: embryonic lethality; arrested development; and small, abnormal or reabsorbing egg cylinders.

27. A method of identifying an agent that modulates ubiquitin ligase E3 gene function, the method comprising:

(a) providing a cell comprising a disruption in an ubiquitin ligase E3 gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates ubiquitin ligase E3 gene function, wherein the agent modulates a phenotype associated with a disruption in an ubiquitin ligase E3 gene.

28. The method of claim 27, wherein the phenotype comprises at least one of the following: embryonic lethality; arrested development; and small, abnormal or reabsorbing egg cylinders.

29. An agent identified by the method of claim 25, claim 26, claim, or claim 27.